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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,218	11/23/1999	A.K. GUNNAR ABERG	4821-362	3537

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/447,218	ABERG ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 18, 2005 (amdt)*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,36,38-40 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 36, 38-40 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/18 & 6/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **1-33, 35, 37 and 41-49** have been cancelled, no claims have been amended, the disclosure has not been amended, and new claim **50** has been added as per the response filed May 18, 2005. Two additional Information Disclosure Statements (2 IDSs) filed May 18, 2005 and June 15, 2005 have been received with all cited references. A declaration signed by William W. Storms, M.D. has also been received with Exhibits A, C and D complete, but with the documents listed on Exhibit B not all bibliographically complete. Documents listed in Exhibits B and D which are bibliographically complete have been cited on the attached PTO-892. But, references E-6, E-9, E-10, E-11 (No dates of publication, some author and publisher information incomplete) could not be made of record because these references did not have complete bibliographic information included for same on either the face of the document or in the listing of references provided by applicant or both. Resubmission is respectfully requested together with the missing bibliographic information preferably printed on a PTO-1449.

Claims **34, 36, 38-40 and 50** remain in the case.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **34, 36, 38-40 and 50** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Berkow et al.** (PTO-892 ref. **R**) in view of **Villani et al. '716** (PTO-1449 ref. **AE**).

The instant claims are directed to the treatment of urticaria (aka hives, a condition associated with allergic reactions) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day. Claim **36** further limits claim **34** by limiting the population of hosts to those "... humans with a higher than normal propensity for or incidence of cancer."

Berkow et al. discloses at p. 333, beginning in the third line under "**Treatment**," that " [s]ymptoms [of urticaria] usually can be relieved with an oral [dose of an] antihistamine ... ."

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19) More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

The findings that
i) Villani et al.'s teaching that DCL and related compounds are known to be effective antihistamines,
ii) the teaching by applicant that DCL has the expected effect in the treatment of urticaria (hives) as predicted by Berkow et al.,
iii) the teaching of dosages ranges which overlap with the claimed dosage ranges, and
iv) the failure of applicant to establish statistically significant unexpected results (no error analysis of the data provided),
when taken together with the disclosure of Berkow et al. are deemed to establish that combination of the instant combination of references is properly motivated. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed May 18, 2005 have been fully considered but they are not deemed to be persuasive.

Applicant argues that in Berkow is not applicable because only first generation antihistamines are listed as examples and furthermore that the prior art teaches that not all antihistaminic agents can be used to treat urticaria. After noting examiner's counter argument that even Berkow acknowledges that not all antihistamines are effective in every patient, applicant further argues that the instant claims are "not obvious because Berkow does not

disclose the use of DCL for the treatment of urticaria, and does not even suggest that all antihistaminic agents are effective in treating urticaria." (emphasis in original) Examiner respectfully disagrees with applicant's conclusion that "... Examiner is in complete agreement with Applicant that Berkow does not render obvious the treatment of urticaria with all known antihistamines." (emphasis in original) Applicant then concludes without more that Berkow is " ... nothing more than an invitation to experiment," without even considering the contents of the other primary reference. Applicant then leaps to the conclusion that because " ... an invitation to experiment is not a proper basis for an obviousness rejection, ... the rejection ... should be withdrawn." Examiner respectfully disagrees with this line of reasoning for the following reasons. First, the standard for obviousness does not require that a single reference must meet the standard for anticipation, i.e. that all elements of a rejection over prior art must be present in a single reference. Second, applicant alleges that the Berkow reference fails because it must teach the specific active ingredient specified by the instant claims. Again this is the standard for anticipation, not the obviousness standard.

Applicant then argues beginning in the first full paragraph of page 6 of the response that Villani does not remedy the deficiencies of Berkow. Applicant then cites at length portion of the Storm declaration to the effect that the side effects attributed by Dr. Storm to DCL were so serious that no one would have considered DCL to be a proper candidate for use as an antihistamine for the treatment of urticaria as of the earliest priority document filing date in 1994. Examiner respectfully disagrees for the following reasons. Looking first at the paragraphs 12-15 of the Storm declaration, examiner notes that applicant's arguments are based on Dr. Storm's explanation of the standards applied to Food and Drug Administration (FDA) proceedings concerning the process of obtaining US government permission to market a pharmaceutical. In particular examiner notes that in paragraph 14, Storm states that " ... I considered reports concerning the adverse effects of one [piperidine] H_1 antagonist to be relevant to the safety of other members of that class." While examiner commends Dr. Storm for his extensive experience in FDA proceeding as documented in his lengthy resume, examiner does not agree that what appears to be a "safe and effective" analysis applies in this forum (before the USPTO); patentability, except where there is clear evidence of inoperability, is an entirely different determination. Applicant's have cited paragraph 17 of the instant declaration, a paragraph which appears to represent the professional opinion of Dr. Storm, but is presented without any data whatsoever to support his allegation that "cardio-toxicity,"

"personality changes" and "tumour growth" are associated with the administration of any level of dosage of DCL. Examiner has carefully reviewed the extensive list of references submitted by Dr. Storm and finds that no combination of these references can provide an adequate factual basis for concluding that DCL is inoperable as an antihistamine. Again examiner emphasizes that the standard for inoperability under 35 U.S.C. §101 is entirely different than those standards applied by the FDA in their proceedings.

Applicant concludes by arguing that the Berkow and Villani references are not properly applied under the statute and therefore that the rejection should be withdrawn. Examiner respectfully disagrees. The rejection has been maintained because the references cited teach generally that antihistamines are useful in the treatment of urticaria (Berkow) and that claims ***3 and 15*** of Villani '716 are directed specifically to the treatment of "allergic reactions," where the quoted term is, according to at least one medical dictionary, a synonym for the term "urticaria."

Examiner has reviewed in detail the declaration of Dr. William Storm. Dr. Storm is clearly knowledgeable in the medicinal antihistamine art, but the instant declaration appears to be beside the point. The instant declaration is of record in an application at the U. S. Patent and Trademark Office (USPTO), not the Food and Drug Administration (FDA). The USPTO is concerned with the disclosure and patenting of inventions, but the USPTO is not in the business of giving permission to market drugs (an FDA matter as suggested by the "safe and effective" language in declaration paragraph 22). Therefore, while Dr. Storm's concerns about side effects would probably be relevant to proceeding before the FDA as suggested by paragraphs 18 and 21 of the instant declaration, these concerns are not relevant to proceedings before the USPTO unless there is a factual disclosure (i.e. a substantial body of relevant test data) that the side effects are real (extrapolation of tests of other compounds, opinions and/or speculations are not enough), that said side effects are actually caused by the pharmaceutical in question, and that said side effects render the pharmaceutical in question completely unable to have the beneficial effect described in a patent claim (i.e. that the invention being claimed is inoperative under 35 U.S.C. §101). Because the instant declaration has not provided an adequate basis to support the conclusion that the prior art (Villani and Berkow) are (or were) inoperative, the instant declaration does not provide a disclosure which is sufficient to support a conclusion that the instant claims are patentable in view of said prior art; i.e. this declaration does not provide an adequate factual basis for disqualification of the cited prior art. Therefore,

examiner concludes that the instant declaration for the most part is not relevant to the question of patentability in the instant case.

Claims **34, 36, 38-40 and 50** are rejected under 35 U.S.C. §103(**a**) as being unpatentable over **Swinyard (II)** (PTO-892 ref. **TA**) and **Swinyard (I)** (PTO-892 ref. **SA**) in view of **Villani et al. '716** (PTO-1449 ref. **AE**) and further in view of **Brandes et al.** (PTO-892 ref. **RA**).

The instant claims are directed to the treatment of urticaria (aka hives) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need thereof and avoidance of the side effects thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day.

Swinyard (II) discloses the utility of H_1-antihistamines in the treatment of urticaria at page 1124, column 1, line 4 of the third paragraph following the heading "Antihistamines." And at page 1130, column 2, this reference discloses the antihistamine azatadine maleate which is a very close structural relative of both loratadine and descarbethoxyloratadine (DCL), sharing with both the identical four ring molecular skeleton and similar antihistamine activity.

Swinyard (I) discloses at pages 778-782 (see page 779, paragraph beginning at column 1) that only certain H_2-antihistamines cause problems with liver P450 enzyme metabolism, but that selection of an alternative H_2-antihistamine is an effective way to avoid this difficulty.

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19) More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

Brandes et al. discloses in the last sentence prior to the "CONCLUSION" that loratadine promotes the growth of two well known neoplasms. This issue is addressed by the instant disclosure at page 24, lines 20-25, with data which is at best incomplete because only one

comparison is made and because there is no statistical error analysis permitting determination of whether the difference suggested by the data is statistically significant.

The motivation to combine the above references is that each is directed to positive and/or negative effects observed following the administration of antihistamines. The primary reference, Swinyard (II) clearly is well motivated in combinations with the remaining references, because this reference discloses all of the side effects commonly associated with H_1-antihistamine administration, and how these may be avoided by substitution of alternative antihistamines, including an antihistamine which is a close structural relative of both loratadine and DCL.

The substitution of DCL for loratadine or its analogue azatadine is deemed to have been an obvious substitution of the ordinary practitioner seeking to optimize the treatment of urticaria as reported in Swinyard (II) in view of the disclosure of Villani et al. that DCL is, like loratadine, also an antihistamine. The additional guidance provided by the Swinyard (I) and Brandes references merely adds to the already extensive discussion in Swinyard (II) of the side effects observed following administration of medicinally appropriate dosages of numerous antihistamines, and therefore would have afforded the ordinary practitioner more than sufficient guidance to make an appropriate determination of whether or not to use DCL to treat urticaria in a given human host in need thereof. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted combination of prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL when appropriate in light of possible side effects, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed May 18, 2005 have been fully considered but they are not deemed to be persuasive.

Beginning at the bottom of page 7 of the instant response applicant argues that Swinyard (II) is an inappropriate reference because " ... while 'enormous number [sic] of clinical conditions for which antihistamine drugs have been suggested,' these drugs 'vary from *effective* to *ineffective* in these conditions,' this [reference] clearly teaches that no

generalization can be made regarding a particular antihistamines efficacy in treating a particular disease, based on a different agent's efficacy." (emphasis in original) Examiner respectfully disagrees with the logic of this argument because again, applicant is asserting that a reference in an obviousness rejection requires meeting the standard of an anticipatory reference. Swinyard (II) is a reference cited in an obviousness rejection, not in an anticipation rejection. And applicant appears to have misstated the teachings of this reference. Examiner notes at page 1124, column 1, third paragraph following the heading **Antihistamines**, Swinyard states that " [t]he majority of these agents are *effective in perennial* and *seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria* and *angioedema, allergic reactions to blood and plasma, dermographism* and as adjuncts to conventional therapy in *anaphylactic reactions*." (italics in original) Therefore, applicant's conclusion that " ... Swinyard (II) would not have suggested that antihistamines in general ... can be used for the treatment of urticaria" is deemed to be a misreading and/or a misunderstanding of Swinyard (II).

In the second full paragraph at page 8 of the instant response, applicant argues that in view of page 590 of Goodman & Gilman (now cited as PTO-892 ref. **XC**) and paragraphs 12-17 of the Storm declaration that the suggestion of parallel pharmaceutical activity based on structural analogy was not properly a basis for alleging motivation to combine references. Applicant notes that allegations made by the Storm declaration as a proper basis for discussion of patentability. Examiner respectfully disagrees, referring applicant to the extensive analysis of the Storm declaration supra wherein examiner concluded that Dr. Storm was applying the "safe and effective" standard of the FDA, a standard not applicable to patentability determinations at the U.S. Patent and Trademark Office. Reviewing the contents of page 590, examiner notes that the last sentence of the second column states that "[t]hese [above noted] side effects are not observed with second generation H_1 antagonists, terfenadine, astemizole and loratadine," suggesting that the arguments of applicant and declarant Storm may be overly pessimistic as well as incomplete.

In the footnote at the bottom of page 8 of the instant response, applicant argues that Brandes is not properly part of the obviousness rejection on the basis that fear of said disclosure would not motivate the ordinary practitioner to use DCL in place of loratadine. Examiner respectfully disagrees, noting that the instant claim **36** includes a specific limitation to hosts less likely to suffer from neoplasms. Applicant's citing fear as a reason to avoid

looking for the facts is puzzling. The facts missing from the instant disclosure, error limits for the data concerning the difference in the ability of loratadine and DCL to promote certain neoplastic tissue growth, is not irrelevant, because said data would tell the ordinary practitioner whether the difference in neoplasm promotion between DCL and loratadine is statistically significant or not, an important consideration in determining how useful DCL would be as a replacement for loratadine, and a fact useful in determining whether claim **36** is properly supported based on the complete facts. Brandes provides an examples of tests against real neoplastic-disease-infected cells while the data in the instant disclosure does not appear to provide a parallel disclosure. Therefore, it is unclear to examiner whether claim **36** is reflective of a real or an imaginary difference in the capacity to promote neoplastic tissue growth in actual neoplasms as disclosed in test results of the Brandes et al. reference. However, examiner maintains that Brandes does suggest that there is a possible prior art basis for the limitation of claim **36** and therefore has been retained in the rejection.

In the first paragraph of page 9 response, citing the Storms declaration applicant argues that " ... those of ordinary skill in the art would not have been motivated to use DCL for the treatment of allergic disorders because prior known [structurally analogous] antihistamines ... were all known to cause serious adverse effects." Examiner respectfully disagrees because applicant and declarant Storms are again relying on a "safe and effective" type of analysis when the current debate is occurring in a non-FDA forum where this analysis is not directed to the appropriate standard. As noted above the standard for "inoperative" under 35 U.S.C. §101 is an entirely different analysis. Examiner remains convinced that the prior art presented by both applicant's representative and declarant Storms, individually or taken in sum, does not appear to require application of this type of analysis and the related rejection under §101.

In the second paragraph on page 9 of the instant response, applicant asserts that "Swinyard (I) and Villani add nothing to the substance of the rejection" initially because Swinyard (I) notes a side effect and that this and other side effects are commonly avoided by substitution of a different antihistamine, and that structurally similar compounds were reported to have similar side effects that the ordinary practitioner would not have been motivated to select DCL as a replacement of any other antihistamine. Secondly applicant argues that because Villani "merely discloses the crude antihistiminic activity of the compounds it discloses, [and] does not even provide that its compounds, much less DCL, can be used for the treatment of urticaria," and thereby implying that Villani is not a proper reference. On the first

argument examiner respectfully disagrees with applicant's conclusion because Swinyard (I) as described by applicant also teaches the freedom to substitute one antihistamine for another, side effects being only one of many reasons (reduced cost, improved selectivity, reduced dosage, etc.) why this might be done by the ordinary practitioner. On the second argument examiner also respectfully disagrees. Applicant is factually incorrect to imply the Villani does not disclose DCL; see Villani '716 at column 26, claim ***3*** wherein the complete chemical structure of DCL is provided And claim ***15*** of Villani '716 is directed to the treatment of "allergic reactions," a generic term which encompasses many conditions including urticaria; see Thomas et al., (PTO-892 reference **T**) wherein "urticaria" is defined at length as a term synonymous with a large and various array of "allergic reaction[s]." And finally applicant's referral to Villani's disclosure of "crude antihistaminic activity [of DCL]" is another reflection of applicant's repeated application of the wrong (FDA "safe and effective") standard as a basis for debating this and other issues. Villani '716's limited disclosure of antihistaminic activity is sufficient to establish that DCL and its fluoro analogue have utility as pharmaceutically active substances with the potential to be effective antihistamines in the treatment of allergic reactions.

Therefore, examiner has maintained this instant grounds of rejection.

Applicant's amendment's have necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published

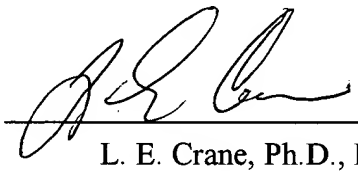
in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
08/02/2005



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